PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 4-32408A	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/02565	International filing date *(day/month/year)* 12.03.2003	Priority date *(day/month/year)* 13.03.2002
International Patent Classification (IPC) or both national classification and IPC A61K9/16		
Applicant NOVARTIS AG et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
10.09.2003	18.06.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Giménez Miralles, J Telephone No. +49 89 2399-8655

Form PCT/IPEA/409 (Cover Sheet) (January 2004)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/02565

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-19 as originally filed

Claims, Numbers

1-21 received on 07.06.2004 with letter of 04.06.2004

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 21

   because:

   ☒ the said international application, or the said claims Nos. 21 relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☒ the claims, or said claims Nos. 21 are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-17
	No:	Claims	18-20
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-20
Industrial applicability (IA)	Yes:	Claims	1-20
	No:	Claims	

2. Citations and explanations

   see separate sheet

Re Item III

1. The present application does not comply with the requirement set forth in Article 34(2)(b) PCT, because the amendments go beyond the disclosure in the international application as filed.

   Step g) of the process claim 1 has been amended to read "separating the microparticles" (i.e. by any method). However, the application as originally filed clearly discloses that said separation is carried out "by sedimentation (optionally by filtration) and freeze-drying", no other alternatives being envisaged. Therefore, the area covered by amended claim 1 unduly extends beyond the original disclosure. The features of amended claims 7 and 8 should be incorporated into claim 1. Therefore, the present International Preliminary Examination Report is established as if this amendment had not been made, i.e. taking claims 1, 7 and 8 in combination (Rule 70.2(c) PCT) [see item V-2 below].

2. A new use claim (claim 21) has been introduced. Support for this claim is alleged to be page 4, lines 22 and 23 of the description. This passage reads "...the addition of which ensures that **the** active ingredient is protected against adsorption on **the** polymer matrix...", which means **the** specific active ingredients and **the** specific polymer matrix of the invention. However, claim 21 is directed to the protection of "**an** active ingredient" (anyone) against adsorption "to **a** polymer matrix" (anyone) without any restriction or limitation, which represents an undue extension (generalisation) of the subject-matter beyond the disclosure of the application as originally filed. Therefore, the present International Preliminary Examination Report is established as if this amendment (new claim 21) had not been made (Rule 70.2(c) PCT).

Re Item V

1. Reference is made to the following documents:

   D1: WO-A-00 03660

   D2: EP-A-0 400 522

D3: WO-A-00 56282

D4: EP-A-0 474 098

D5: US-A-5 869 103 (cited in the application)

D6: EP-A-0 998 917

2. Claims 1-17 (process)

2.1 Novelty

Claims 1-17 appear to comply with the requirement of Article 33(2) PCT. The process consisting of steps a) to g) [see item III-1 above], in particular step d) according to which the first emulsion is formed using a gear pump, is not anticipated in the available prior art.

2.2 Inventive step

D1 and D3 represent the closest prior art for the process claims 1-17. Both documents disclose a double emulsion solvent evaporation method followed by removal of the organic solvent for the preparation of microspheres from biodegradable polymers encapsulating a pharmaceutically active substance, wherein the first water-in-oil emulsion is prepared by using mechanical agitation, ultrasonic energy, nozzle atomization, static mixers, impeller mixers, vibratory mixers (see D1: p.16, l.12-15), or a homogeniser (see D3: example 1). Present claims 1-17 differ from D3 in that: i) the first water-in-oil emulsion is prepared using a gear pump; and ii) the subsequent water-in-oil in water emulsion is produced in a static mixer. Both equipments (gear pump and static mixer technologies) are well known in the art (see e.g. D6: fig. 3). It has not been demonstrated yet why the skilled person would not contemplate the use of a gear pump to form the first water-in-oil emulsion as an obvious alternative to other kind of customary mixing and/or homogenising devices. Therefore, an inventive step cannot be acknowledged.

3. Claims 18-20 (product by process)

3.1 Novelty

Claims 18-20 do not comply with the requirement of Article 33(2) PCT. D3 discloses microparticles comprising a polymeric matrix, an active agent (e.g. antigenic proteins) and a phospholipid (see p.3, l.21-35). The polymeric material comprises a biodegradable polymer, e.g. PLA or PLGA (see p.5, l.1-5), and a

water-soluble polymer, e.g. PVA or dextran (see p.5, l.24-26; p.8, l.25-36; example 1). The fact that the phospholipid is claimed in D3 to function as an immunostimulant whereas in the present application the phospholipid is claimed to be a "water insoluble surface active substance" is totally irrelevant for the assessment of novelty. Further, the feature "wherein the microparticles are obtained according to a process of any one of claims 1 to 17" cannot be seen as a distinguishing feature of the microparticles themselves. Claims for products defined in terms of a process of manufacture are only admissible if the products as such fulfil the requirements for patentability, i.e. inter alia that they are new and inventive. A product is not rendered novel merely by the fact that it is produced by means of a new process. Therefore, D3 anticipates all the features defined in claims 18-20.

3.2 Inventive step

For the assessment of inventive step, following documents are relevant: D1, D2, D4 and D5. D1 discloses features a), b) and d) as claimed in claim 18. The difference is that no water soluble polymer is disclosed in D1 (see example 1). It is the same for D2 (see p.5, l.41 - p.6, l.4). However, the incorporation of feature c) (water soluble polymer) into D1 or D2 would be obvious for the skilled person aiming at accelerating release of the active ingredient through formation of porous structures in the polymer matrix in the light of the prior art. Thus, D4 discloses the combination of a PLA and PVP to form a controlled release polymeric matrix for e.g. microcapsules (see p.2, l.49 - p.3, l.37); fig. 2 clearly shows that increasing the amount of PVP in the PLA/PVP matrix results in faster release of the active ingredient. D5 discloses the combination of PLG and PEG or poloxamers for the same purpose (see col. 4, l.4-30; col. 6, l.54-60). Accordingly, no inventive contribution can be seen in the subject-matter of present claims 18-20.

What is claimed is:

1. A process for the preparation of microparticles comprising the steps
   a) preparation of an aqueous solution of at least one pharmacologically active ingredient
   b) preparation of a solution of a biodegradable polymer, a water soluble polymer, and a surface active substance in an organic solvent which is insoluble in water,
   c) preparation of an aqueous solution of a surfactant,
   d) mixing solution a) and b) using a gear pump to form an emulsion,
   e) pumping emulsion d) and the aqueous solution c) with a gear pump to a static mixer and mixing them in the static mixer to form a water in oil in water emulsion,
   f) removing the organic solvent from emulsion e), and
   g) separating the microparticles.

2. The process of claim 1 wherein the surface active substance of step b) is a phospholipid or lecithin.

3. The process of claim 1 or 2 wherein a phosphate buffer is used for the preparation of the aqueous solutions of step a) and c).

4. The process of any one of claims 1 to 3 wherein the organic solvent of step c) is methylene chloride.

5. The process of any preceding claim wherein the surfactant of step c) is polyvinyl alcohol.

6. The process of any preceding claim wherein the organic solvent in step f) is removed by evaporation.

7. The process of any preceding claim wherein the microparticles on step g) are separated by sedimentation or filtration.

8. The process of any preceding claim wherein the obtained microparticles are freeze-dried.

9. The process according to any one of claims 2 to 8 wherein the amount of phospholipid or lecithin is from about 0.01 to about 90% w/w of the final microparticle weight.

10. The process according any preceding claim wherein the biodegradable polymer is chosen from at least one of homo- or copolyester of dicarboxylic acid, alkylene diol, polyalkylene glycol and/or aliphatic hydroxycarboxylic acid; homo- or copolyamide of dicarboxylic acids, alkylene diamine and/or aliphatic aminocarboxylic acid; corresponding polyester-polyamide copolymer; polyanhydride; polyorthoester; polyphosphazene; and polycarbonates.

11. The process of claim 10 wherein the biodegradable polymer is poly-L- or poly-D,L-lactic acid or poly-D,L-lactide/glycolide with a monomer ratio of ca. 1:1 and a molecular weight of 5000 to 100,000 daltons.

12. The process according to any preceding claim wherein the water soluble polymer is polyvinyl pyrrolidone.

13. The process according to any one of claims 2 to 12 wherein the phospholipid is phosphatidyl choline.

14. The process according to any preceding claim wherein the active ingredient is a peptide, a polypeptide or a protein.

15. The process of claim 14 wherein the active ingredient is selected from at least one of antibodies, growth hormones, insulin, interferons, erythropoietin, calcitonin, heparin, somatostatins, cell-stimulating factors and parathyroid hormones.

16. The process according to claim 15 wherein the interferon is interferon alpha 2b.

17. The process according to any preceding claim wherein the organic solvent is removed from the microparticles using cross-filtration technology by

a) circulating emulsion e) tangentially to a membrane at a constant flow wherein the organic solvent, salts and excipients are removed through the membrane,

b) replacing water removed through the membrane by fresh water.

18. Microparticles comprising
    a) a pharmaceutically active ingredient,
    b) at biodegradable polymer,
    c) a water soluble polymer,
    d) a phospholipid or lecithin

    wherein the microparticles are obtained according to a process of any one of claims 1 to 17.

19. Microparticles according to claim 18 having a diameter of 0.1 to 200 µm.

20. Microparticles according to claim 18 or 19 containing 1 to 20% by weight active agent, based on the weight of the microparticles.

21. Use of a phospholipid or lecithin to protect an active ingredient against adsorption to a polymer matrix.